Pathophysiology of Type 2 Diabetes and Its Treatment Policy

Kohei KAKU*1

Abstract
Impaired insulin secretion and increased insulin resistance, the main pathophysiological features of type 2 diabetes, jointly contribute to the development of this disease. Recently, it has become widely recognized that the functional pancreatic β cell mass decreases over time and type 2 diabetes is a progressive disease. Studies suggest the possibility that the Japanese may have many genes susceptible to diabetes including thrifty genes. Various environmental factors, added to these genetic factors, are considered responsible for the onset of disease, and the number of patients is increasing rapidly reflecting recent lifestyle changes. Impaired insulin secretion is characterized by lowered glucose responsiveness. In particular, the decrease in postprandial-phase secretion is an essential pathophysiological condition. Glucolipotoxicity, if left untreated, results in the decrease in the functional pancreatic β cell mass. The goal of diabetes treatment is to secure a quality of life (QOL) and lifespan comparable to those of healthy people, and a prerequisite for this is the prevention of onset and progression of vascular complications. The need for earlier initiation of proactive intervention must be emphasized, as well as the importance of comprehensive (blood sugar, blood pressure, and lipids) intervention in attaining this goal.

Key words Type 2 diabetes, Impaired insulin secretion, Insulin resistance

Introduction
Diabetes is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from insufficient action of insulin. The main pathophysiological features of type 2 diabetes, which represents a great majority of diabetic cases in Japan, are impaired insulin secretion and increased insulin resistance. The impairment of pancreatic β cell function notably shows progression over time.

Etiology and Pathophysiology of Type 2 Diabetes

Etiology
Type 2 diabetes is caused by a combination of genetic factors related to impaired insulin secretion and insulin resistance and environmental factors such as obesity, overeating, lack of exercise, and stress, as well as aging. It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents. A fact considered important in pathogenesis is that Japanese show lower insulin secretory capacity after sugar loading, suggesting smaller potential for pancreatic β cell function than Western people. It has also been pointed out that Japanese individuals may have many diabetes-sensitive genes including thrifty genes. The number of diabetic patients is increasing rapidly reflecting the changes in lifestyle (Fig. 1).

Genetic factors involved in the pathogenesis of diabetes
The development of type 2 diabetes is clearly associated with a family history of diabetes. The

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significantly higher concordance rate between monozygotic twins than between dizygotic twins suggests the considerable involvement of genetic factors.¹ The pathogenesis has been assumed to involve genetic abnormality in the molecules related to the regulatory system of glucose metabolism. The analyses of candidate genes targeted at glucose-stimulated insulin secretion of pancreatic β cells and the molecules comprising the molecular mechanism for insulin action have identified genetic abnormalities that can be independent causes of pathogenesis, including those in glucokinase genes, mitochondrial genes, and insulin receptor genes. Recently, a genome-wide association study (GWAS) has identified the mutation in the KCNQ1 gene related to insulin secretion abnormality as an important disease-susceptible gene associated with the pathogenesis of diabetes in Asian ethnic groups including the Japanese.²

The genetic abnormalities reported so far, all combined, explain about 30% of the genetic factors for diabetes, and our understanding of genetic factors is expected to be practically complete in the near future. According to the current classification of disease types, diabetic cases with identified genetic abnormality are classified under “those due to other specific mechanisms or diseases.”

Roles of environmental factors
Aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc. are independent risk factors of pathogenesis. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass, induces insulin resistance, and is closely associated with the rapid increase in the number of middle- and high-aged patients. The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance. Even mild obesity (BMI < 25) causes a 4- to 5-fold increase in the risk of developing diabetes, if accompanied by the increase in visceral fat mass. The Japanese are prone to visceral

Table 1 Factors causing increase in visceral fat

<table>
<thead>
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<th>1. Stress-related factors</th>
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<td>• Overeating, especially excessive intake of simple sugars</td>
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<td>• Smoking</td>
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<td>• Increase in alcohol intake</td>
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<tr>
<td>• Disorders of nervous and endocrine systems: increase in cortisol, abnormality in sex hormone secretion</td>
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<td>2. Lowered energy consumption due to a lack of exercise</td>
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<td>3. Genetic factors</td>
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<td>4. Aging</td>
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Fig. 1 Etiology and pathophysiology of type 2 diabetes in Japanese

![Diagram showing etiology and pathophysiology of type 2 diabetes in Japanese.](Diagram)
fat accumulation due to hyperalimentation, and risk factors for diabetes are linked to the accumulation of visceral fat (Table 1).

Pathophysiology

Impaired insulin secretion and insulin resistance contribute more or less jointly to the development of pathophysiological conditions.

Impaired insulin secretion

Impaired insulin secretion is a decrease in glucose responsiveness, which is observed before the clinical onset of disease. More specifically, impaired glucose tolerance (IGT) is induced by a decrease in glucose-responsive early-phase insulin secretion, and a decrease in additional insulin secretion after meals causes postprandial hyperglycemia. An oral glucose tolerance test (OGTT) in IGT cases generally indicates an over-response in Western and Hispanic individuals, who have markedly high insulin resistance. On the other hand, Japanese patients often respond to this test with decreased insulin secretion. Even when an over-response is seen in persons with obesity or other factors, they show a decrease in early-phase secretory response. The decrease in early-phase secretion is an essential part of this disease, and is extremely important as a basic pathophysiological change during the onset of disease in all ethnic groups.

Impaired insulin secretion is generally progressive, and its progression involves glucose toxicity and lipo-toxicity. When untreated, these are known to cause a decrease in pancreatic \( \beta \) cell mass in animal experiments. The progression of the impairment of pancreatic \( \beta \) cell function greatly affects the long-term control of blood glucose. While patients in early stages after disease onset chiefly show an increase in postprandial blood glucose as a result of increased insulin resistance and decreased early-phase secretion, the progression of the deterioration of pancreatic \( \beta \) cell function subsequently causes permanent elevation of blood glucose (Fig. 2).

Insulin resistance

Insulin resistance is a condition in which insulin in the body does not exert sufficient action proportional to its blood concentration. The impairment of insulin action in major target organs such as liver and muscles is a common pathophysiological feature of type 2 diabetes. Insulin resistance develops and expands prior to disease onset.

The investigation into the molecular mechanism for insulin action has clarified how insulin resistance is related to genetic factors and environmental factors (hyperglycemia, free fatty acids, inflammatory mechanism, etc.). Known genetic factors, include not only insulin receptor and insulin receptor substrate (IRS)-1 gene polymorphisms that directly affect insulin signals but also polymorphisms of thrifty genes such as the \( \beta \), adrenergic receptor gene and the uncoupling protein (UCP) gene, associated with visceral obesity and promote insulin resistance. Glucolipotoxicity and inflammatory mediators are also important as the mechanisms for impaired insulin secretion and insulin signaling impairment.

Recent attention has focused on the involvement of adipocyte-derived bioactive substances (adipokines) in insulin resistance. While TNF-\( \alpha \), leptin, resistin, and free fatty acids act to increase resistance, adiponectin improves resistance.

Clinical tests to assess the extent of insulin resistance include homeostasis model assessment for insulin resistance (HOMA-IR), insulin sensitivity test (loading test), steady-state plasma glucose (SSPG), minimal model analysis, and insulin
The Matsuda index is now gaining recognition as a relatively simple procedure that can simultaneously evaluate insulin resistance in the liver and muscles. After performing OGTT, this index is calculated by the formula:

\[
\text{Matsuda Index} = \frac{10,000}{\sqrt{\text{FPG} \times \text{FPI}}} \times (\text{mean PG} \times \text{mean PI}),
\]

where FPG is fasting plasma glucose and FPI is fasting plasma insulin.

A more convenient way to estimate the degree of resistance is to check for the presence of high fasting blood insulin, visceral obesity, hypertriglyceridemia, etc.

**Treatment Policy for Type 2 Diabetes**

The goal of diabetes treatment is to secure a quality of life (QOL) and lifespan comparable to those of healthy people, and a prerequisite for attaining this goal is the prevention of onset and progression of vascular complications. The risk of macrovascular disease such as cardiovascular disorders (atherosclerotic lesions) is increased already in individuals with marginal blood glucose levels, underscoring the need for early intervention.

### Effective treatment to control vascular complications

Reports on the interventions to prevent the onset of diabetes, control complications, and improve prognosis have demonstrated the following facts:

1. Lifestyle improvement and anti-diabetic drugs (α-glucosidase inhibitor, metformin, thiazolidine) to treat IGT suppress the risk of developing type 2 diabetes,\(^5\)–\(^7\)
2. SU drugs, metformin, and insulin are effective in controlling both microvascular disease and macrovascular disease, and earlier intervention is essential to the control of macrovascular disease.\(^8\)–\(^11\)
3. Comprehensive intervention including blood pressure and lipid management is extremely effective in controlling vascular complications and reducing mortality rate.\(^12\),\(^13\)
4. Pioglitazone suppresses the recurrence of cardiovascular disorders.\(^14\)

Earlier and more comprehensive (including blood glucose, blood pressure, and lipid) intervention is more effective in controlling vascular complications and improving prognosis.

**The treatment paradigm for type 2 diabetes**

Early initiation of intervention is also important for curbing the progression of pathophysiological conditions. Early efforts to remove the effect of glucose toxicity as much as possible and to preserve pancreatic β cell function are essential prerequisites for long-term management of diabetes. Microvascular disease is more closely associated with long-term blood glucose control. The treat-
The treatment paradigm needs to be considered from the viewpoints of not only controlling vascular complications but also preventing the progression of pathophysiological conditions. In this sense, it is necessary to move up the treatment schedule (Fig. 3). Ideally, the aim should be to prevent the onset of diabetes among individuals with IGT (primary prevention). In addition to proactive intervention for lifestyle improvement, we need to accelerate the debate about whether to use pharmacological intervention.

**The flow of treatment**

The treatment algorithm for type 2 diabetes recommended in Europe and the U.S., based on the results of United Kingdom Prospective Diabetes Study (UKPDS), aims at cost-effective care in which lifestyle improvement and metformin
are started at the same time and patients showing poor response are subsequently treated with the additional use of SU drugs and insulin therapy. On the other hand, the common practice in Japan is to select appropriate oral hypoglycemic agents when the patient has failed to achieve the blood glucose control target despite sufficient patient education on the nature of diabetes and dietary therapy and exercise therapy for 2 to 3 months. There are five groups of oral agents currently in use: SU drugs, fast-acting insulin secretion stimulators (glinides), biguanides, thiazolidines, and α-glucosidase inhibitors—some of these are the drugs developed after UKPDS. In view of the difference between Japanese and Western populations in the pathophysiological features of diabetes, and considering our own stance on the importance of early initiation of strict blood glucose control is the presence or absence of complications. Since disease control status as seen from blood glucose levels, present and past obesity, and the drugs developed after UKPDS. In view of the difference between Japanese and Western populations in the pathophysiological features of diabetes, and considering our own stance on the other diseases. Earlier intervention and continued treatment are the keys to achieving the treatment goals. The importance of close collaboration between specialists and non-specialist physicians continues to increase.

The important elements in determining treatment policy include history taking, the present disease control status as seen from blood glucose and HbA1c levels, present and past obesity, and the presence or absence of complications. Since early initiation of strict blood glucose control is important, the use of anti-diabetic agents should not be delayed. The flow of treatment and the suggestions on the use of drugs are summarized in Fig. 4.

The recent results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study indicate the possibility that abrupt intensive therapy may occasionally lead to poor prognosis. On the other hand, intensive therapy has been reported to achieve better control of cardiovascular risk in the patients with a shorter history of illness. The treatment of patients with long-standing illness and a long history of poor blood glucose control, as well as those with advanced vascular damage, should aim at gradual improvement of blood glucose control rather than a rapid decrease to HbA1c <6%.

Conclusion

With the soaring number of patients reflecting population aging, diabetes demands broader involvement of non-specialist physicians than other diseases. Earlier intervention and continued treatment are the keys to achieving the treatment goals. The importance of close collaboration between specialists and non-specialist physicians continues to increase.

References